Factors Affecting Health Care Utilization for Children in Japan
Yasushi Ishida, Sachiko Ohde, Osamu Takahashi, Gautam A. Deshpande, Takuro Shimbo, Shigeaki Hinohara and Tsuguya Fukui
Pediatrics 2012;129;e113; originally published online December 26, 2011;
DOI: 10.1542/peds.2011-1321

Int J Hematol (2011) 93:633–644
DOI 10.1007/s12185-011-0843-6

ORIGINAL ARTICLE

Social outcomes and quality of life of childhood cancer survivors in Japan: a cross-sectional study on marriage, education, employment and health-related QOL (SF-36)

Yasushi Ishida · Misato Honda · Kiyoko Kamibeppu · Shuichi Ozono · Jun Okamura · Keiko Asami · Naoko Maeda · Naoko Sakamoto · Hiroko Inada · Tsuyako Iwai · Naoko Kakee · Keizo Horibe

Received: 19 February 2011 / Revised: 28 March 2011 / Accepted: 29 March 2011 / Published online: 26 April 2011

Abstract Social outcomes and quality of life (QOL) of childhood cancer survivors (CCSs) remain unknown in Japan. We investigated these outcomes in young adult CCSs compared to those of their siblings in Japan, and analyzed the association between social outcome and SF-36 health survey subscale scores. Between 2007 and 2009, we performed a cross-sectional survey using self-rating questionnaires. We estimated social outcomes and health-related QOL by performing the SF-36 in each group: CCSs with or without stem cell transplantation (SCT)/radiotherapy (RT) and their siblings. Adjusted odds ratios for outcomes of interest were estimated using logistic regression analysis. Questionnaires from 185 CCSs and 72 CCS's siblings were analyzed. There were no differences in educational attainment or annual income. The SF-36 subscale scores of CCSs with SCT and RT were significantly lower than those of siblings in physical functioning (PF) ($p < 0.001$ and 0.003, respectively) and general health (GH) (both $p = 0.001$). Lower PF scores correlated with recurrence ($p = 0.041$) and late effects ($p = 0.010$), and poor GH scores with late effects ($p = 0.006$). The CCSs had made efforts to attain educational/vocational goals; however, a significant proportion of CCSs who had experienced late effects remain at increased risk of experiencing diminished QOL.

Keywords Childhood cancer survivors · Marriage · Education · Employment · Health-related QOL · SF-36

Electronic supplementary material The online version of this article (doi:10.1007/s12185-011-0843-6) contains supplementary material, which is available to authorized users.

Y. Ishida (✉)
Department of Pediatrics, St. Luke's International Hospital, 10-1 Akashi-cho, Chuo-ku, Tokyo 104-0044, Japan
e-mail: yaishida@luke.or.jp

M. Honda
Department of Pediatrics, Ehime University Graduate School of Medicine, Toon, Japan

K. Kamibeppu
Department of Family Nursing, The University of Tokyo, Tokyo, Japan

S. Ozono · H. Inada
Department of Pediatrics, Kurume University School of Medicine, Fukuoka, Japan

J. Okamura
Institute for Clinical Research, National Kyushu Cancer Center, Fukuoka, Japan

K. Asami
Department of Pediatrics, Niigata Cancer Center Hospital, Niigata, Japan

N. Maeda · K. Horibe
Department of Pediatrics, Center for Clinical Research, Nagoya Medical Center, Aichi, Japan

N. Sakamoto
Department of Epidemiology, National Research Institute for Child Health and Development, Tokyo, Japan

T. Iwai
Department of Hemato-Oncology, Kagawa Children's Hospital, Kagawa, Japan

N. Kakee
Department of Health Policy, National Research Institute for Child Health and Development, Tokyo, Japan

1 Introduction

As a result of advances in treatment, 70–80% of children diagnosed with cancer become long-term survivors. In Japan, the estimated number of pediatric cancer survivors is upward of 50,000, or approximately one in 700 adults between the ages of 20 and 39 years. Although an increased number of children with cancer have been cured, many survivors experience various health problems or late effects as a result of their treatments [1, 2]. In addition to various physical problems in childhood cancer survivors (CCSs) [3], social outcomes vis-à-vis marriage, education and employment are apparently affected by these late effects, either directly or indirectly. An increasing number of studies have focused on the social outcomes of CCSs [4–12].

A Swedish population-based study [4] revealed that central nervous system (CNS) tumor survivors had poorer social outcomes compared to the general population, whereas outcomes for non-CNS cancer survivors were similar to those of the general population. On the other hand, the results of the Childhood Cancer Survivor Study (CCSS) suggest that CCSs generally have high school graduation rates similar to those in the general population, but they are slightly less likely to attend college; they are also more likely to be unemployed and not married as young adults [5]. Johannsdottir et al. [6] also outline important differences in social outcomes (i.e., employment and parenthood) between CCS and controls early in adult life.

The health-related quality of life (QOL) of CCSs has been studied extensively using the 36-item Short Form Health Survey (SF-36). Reulen et al. [13] demonstrated the validity and reliability of the SF-36 when used with CCSs, but they point out that ceiling effects should be recognized for researchers in using the SF-36 with CCSs. Maunsell et al. [14] show that QOL differences between CCSs and controls are small, and for the most part are probably not clinically important. In their study, survivors' scores on most subscales of the SF-36 were similar to those of controls, despite experiencing some difficulties in their daily activities [15].

Many reports including meta-analyses or systematic reviews of social outcomes [16] and QOL [17, 18] among CCSs have been published; however, the association between social outcomes and SF-36 scores remains to be elucidated [12, 19]. We have already reported that both stem cell transplantation (SCT) and radiotherapy (RT) are closely associated with the late effects of CCSs [20, 21] and that no significant differences are found between CCSs and siblings in terms of depression and anxiety, but CCSs have significantly more posttraumatic stress symptoms and greater posttraumatic growth [22]. In this article, we investigated the social outcomes and QOL of young adult CCSs with or without SCT/RT compared to those of their siblings in the same population, and analyzed the association between social outcomes and SF-36 subscale scores.

2 Patients and methods

2.1 Study design and participants

We performed a cross-sectional survey involving self-rating questionnaires vis-à-vis the social outcomes and QOL of CCSs, compared to those of the siblings [20, 23]. The study was conducted between 1 August 2007, and 31 March 2009. The subjects were divided into three groups: the CCS with or without SCT/RT, and siblings. The last group was considered as a control that matched with the CCSs with regard to genetic capabilities and environmental similarity. The CCS and their siblings were recruited from the participating hospitals listed in the supplemental appendix 1.

The eligibility criteria for CCSs and their siblings were as follows: (1) the subjects were 16 years old or older at the time of the survey, (2) CCSs had been diagnosed with cancer at 18 years of age or younger, (3) CCSs had been in continuous remission for more than 5 years since cancer diagnosis without any additional need for anticancer therapy, (4) they had been informed about their diagnoses, and (5) informed consent was provided by both CCSs/siblings and their guardians. If CCSs had two or more siblings, we selected the subject with the nearest age to the CCSs among the siblings. The exclusion criteria were as follows: (1) the attending physicians believed that the survey would cause an undesirable effect on CCSs, (2) the subjects had some underlying disease besides cancer that affected their social outcome or QOL, or (3) the subjects were unable to answer the questionnaires by themselves.

2.2 Methods

After obtaining appropriate informed consent, the CCSs were provided with an anonymous questionnaire by the attending pediatricians and asked to return it within post-one month. The patients' clinical records were reviewed to analyze cancer-related variables, including the diagnosis, birth year and month, age at diagnosis, age at therapy completion, time since diagnosis, treatment variables and the late effects of CCSs observed at the time of the survey. We used an encrypted numbering system for dispatching data to the principal investigator, to maintain the confidentiality of patient information. Late effects were defined as adverse events that were grade 2 (i.e., symptomatic or needing some intervention) or higher, according to the

Common Terminology Criteria for Adverse Events, v. 3 (CTCAEv3), which was originally developed by the National Cancer Institute (Japanese CTCAE v. 3.0 by JCOG and JSCO, http://www.jcog.jp/).

2.3 Measurement of variables

The questionnaire consisted of 220 items, with three items involving free writing. We evaluated seven background items (Q1), two truth-telling-related items (Q2), seven lifestyle-associated items (Q3), nine items related to medical visits to the hospital (Q4), four general health-related items (Q5), six past operation and drug usage history items (Q6), seven daily habit items (Q7), nine pregnancy and delivery history items (Q8), 72 subjective physical dysfunctions items (Q9), 36 SF-36-related items (Q10), 64 psychosocial problems-related items (Q11) and three free-writing items (Q12).

In this article, we focus on Q3 and Q10. Q3 contained seven items relating to lifestyle, marital status, educational achievements, current employment, work status, working ability (frequency of absence) and annual income in the last year. Q10, comprising 36 SF-36 items, was often used to measure health-related QOL outcomes [24]. The SF-36 is a generic self-report measure that evaluates eight subscales that represent different aspects of well-being, with respect to eight physical and mental health dimensions in Table 1: physical functioning (PF), bodily pain (BP), role limitations caused by physical health problems (RP), role limitations caused by personal or emotional health problems (RE), general mental health (MH), social functioning (SF), vitality (VT) and general health perception (GH). It also involves two summary scales: the mental component score (MCS) and the physical component score (PCS). Multi-item subscales are scored on a 0–100 percentage scale, with higher scores representing higher levels of functioning and health. Data were presented as *T* scores, with a mean score of 50 and a standard deviation (SD) of 10. *T* scores were dichotomized, in which a *T* score below the population score (i.e., the respective nation's norm, while matching for both age and gender in 2007 [25]) indicated a respondent as having reported poor health-related QOL (HR-QOL). Interpretation guidelines link SF-36 subscales and summary scores to the probability of outcomes, allowing scores to be used as predictors of morbidity (physical and mental) and health-care utilization. SF-36 and summary scores have been extensively tested for reliability and validity [26]. The Cronbach's alpha coefficient of SF-36 was found to be 0.79 (CCSs only) and 0.71 (CCSs and siblings) in this study.

In terms of marital status, subjects were categorized as married, never married and others (i.e., divorced or remarried), while educational achievement was classified as follows: lower than high school, high school graduate, college or vocational school graduate, and university or graduate school graduate. Further, employment status was classified as follows: company desk workers ("white collar"); part-time workers; those with medical jobs; industrial workers ("blue collar"); homemakers; those who were unemployed, including those on job training; and others. In terms of annual income, each subject was classified into one of five categories: less than 1 million Japanese yen (JPY), 1–2 million JPY, 2–3 million JPY, 3–5 million JPY and 5 million JPY or more.

2.4 Ethical issues

The study was performed in accordance with the Declaration of Helsinki and was approved by the ethics committee of the principal investigator's institution (Y. Ishida, Ehime University Graduate School of Medicine and St. Luke's International Hospital). The study was also approved by the local ethics committees of all the participating hospitals, prior to initiation.

2.5 Statistical analysis

We estimated the prevalence of outcomes among CCSs with or without SCT/RT and the siblings group. Three primary outcomes were assessed: (1) social outcomes and (2) general QOL according to SF-36 scores between each pair groups (i.e., CCSs and siblings, CCSs with SCT and CCSs without SCT, CCSs with RT and CCSs without RT), and (3) the association between social outcomes and SF-36 scores (for the CCS group only). We performed χ^2 tests or a Fisher exact test (for any cells with expected counts <5) within categorical predictors, and the *t* test or Kruskal–Wallis methods for continuous variables. As for cross-table comparisons, we used adjusted standardized residuals to evaluate the difference between the observed and expected values; the columns which gave more than 1.96 of adjusted standardized residual were considered as significant [27]. The adjusted odds ratios (ORs) for adverse outcomes were estimated by employing logistic regression analysis. As adjusted variables, we selected independent, significant risk factors such as SCT, solid tumors, recurrence and duration after therapy completion, as shown in our previous article. To avoid multi-collinearity, we assessed associations between predictors in a pairwise fashion. Data were analyzed through the use of SPSS software, v. 18.0 (SPSS IBM Japan Inc., Tokyo, Japan).

We planned a study of independent CCSs and siblings, with five CCSs per sibling. The results of a previous study [3] indicate that the probability of chronic health conditions among siblings is 0.35. If the true probability of chronic health conditions among CCSs is 0.60, we would need to

Table 1 Information of the SF-36 subscales and summary scores [25]

Name of subscale	No. of items	Summary of contents
Physical component score (PCS)		
Physical functioning (PF)	10	Extent to which health limits physical activities such as self-care, walking, climbing stairs, bending, lifting, and moderate and vigourous exercises
Role limitations caused by physical health problems (RP)	4	Extent to which physical health interferes with work of other daily activities, including accomplishing less than that required, limitations in the kind of activities or difficulty in performing activities
Bodily pain (BP)	2	Intensity or pain and effect of pain on normal work, both inside and outside the home
General health perception (GH)	5	Personal evaluation of health, including current health, health outlook and resistance to illness
Mental component score (MCS)		
Vitality (VT)	4	Feeling energetic and full of pep versus feeling tired and worn out
Social functioning (SF)	2	Extent to which physical health or emotional problems interfere with normal social activities
Role limitations caused by personal or emotional health problems (RE)	3	Extent to which emotional problems interfere with work or other daily activities, including decreased time spent on activities, accomplishing less and not working as carefully as usual
General mental health (MH)	5	General mental health, including depression, anxiety, behavioral–emotional control, general positive affect

study 180 case patients and 36 control patients to be able to reject the null hypothesis that the outcome rates for CCSs and siblings are equal with a power of 0.8 ($\beta = 0.2$) and a type I error probability (α) of 0.05. We therefore used an uncorrected χ^2 statistic to evaluate this null hypothesis. In addition, the number needed to analyze nine determinants via multivariate logistic regression methods—to determine the risk factors for late effects—was estimated as 180 for CCSs.

3 Results

The demographic data of the participants are shown in Table 2. Among the CCSs, 189 returned the questionnaires (response rate 72%). Of these, four subjects were excluded because two of the four had an underlying disease besides cancer that affected their QOL, one questionnaire had been completed by the patient's mother and one CCS was 20 years old at diagnosis. We also excluded two questionnaires from siblings, because they were 14 and 15 years of age at the time of survey. The mean age at diagnosis was 8.3 years (SD 4.8) for female CCSs and 8.5 years (SD 5.0) for male CCSs. The proportion of those aged 16–19 years was a little smaller in the siblings group than in the CCSs group. With regard to the primary cancers involved, acute lymphoblastic leukemia comprised 43.9% of the CCSs, followed by acute myeloid leukemia/myelodysplastic syndrome (13.3%) and lymphoma (12.3%). A total of 128 cases of primary cancers were hematological, followed by brain tumors (10 cases), bone/soft tissue sarcoma (18 cases) and other solid tumors (29 cases). As for treatment of the primary cancer, 98% of the CCSs received chemotherapy, 61%, RT, 38% surgery; and 25% hematopoietic SCT. Among the CCSs, one or more late effects were found in 56%, two or more late effects in 17% and three or more in 6%.

The current social outcomes between each pair groups are shown in Table 3. The proportion of subjects living with a partner was higher and that living with parents was lower significantly in the sibling group, because the marriage rate within the female sibling group was high (36%). The marriage rate was especially high in the younger than 24 years of age group for siblings; however, the marriage rate was quite similar in the 25 years or more age group. There were also no large differences in educational attainment; the CCSs revealed a higher proportion of high school level and the CCS with SCT showed a higher proportion of university/graduate school level. The unemployment rate tended to be a little high in the CCSs, especially CCSs with SCT or RT compared to the siblings. The proportion of company desk workers ("white collar") was significantly higher in the sibling group compared to the CCSs. Of particular importance was the high proportion of CCSs holding medical jobs: 15% for females and 7% for males. Finally, there were no large differences in working

Table 2 The demographical data of participants

	Total CCS ($n = 184$)	Siblings ($n = 72$)	t test or χ^2 (p value) CCS versus siblings	CCS with SCT ($n = 46$)	CCS without SCT ($n = 138$)	t test or χ^2 (p value) SCT versus no SCT	CCS with RT ($n = 113$)	CCS without RT ($n = 72$)	t test or χ^2 (p value) RT versus no RT
Gender (female)	108 (58%)	42 (58%)	0.995	27 (59%)	81 (58%)	0.960	68 (60%)	40 (56%)	0.534
Age at diagnosis (median)	8.3 ± 4.8 (8)			10.1 ± 4.4 (10)	7.7 ± 4.8 (7)	0.003	8.6 ± 4.8 (8)	7.9 ± 4.9 (7)	0.350
0–5 years of age	60 (32%)	–		10 (22%)	50 (36%)[a]	0.036	37 (33%)	23 (32%)	0.256
6–10 years of age	50 (27%)	–		10 (22%)	40 (29%)		26 (23%)	24 (33%)	
≥11 years of age	75 (41%)	–		26 (57%)[a]	49 (35%)		50 (44%)	25 (35%)	
Age at survey (median)	23.1 ± 4.9 (22)	24.9 ± 5.1 (24)	0.001	22.9 ± 4.8 (22)	23.2 ± 5.0 (22)	0.659	24.1 ± 5.0 (23.5)	21.6 ± 4.5 (21)	0.001
16–19 years of age	47 (25%)[a]	7 (10%)	0.040	11 (24%)	36 (26%)	0.566	21 (19%)	26 (36%)[a]	0.026
20–24 years of age	75 (40%)	19 (41%)		19 (41%)	56 (40%)		46 (41%)	29 (40%)	
25–29 years of age	38 (21%)	12 (26%)		12 (26%)	26 (19%)		27 (24%)	11 (15%)	
≥30 years of age	25 (14%)	4 (9%)		4 (9%)	21 (15%)		19 (17%)	6 (8%)	
Duration after therapy cessation									
0–4 years	5 (3%)	–		3 (7%)	2 (1%)	0.003	4 (4%)	1 (1%)	0.255
5–9 years	50 (27%)	–		19 (41%)[a]	31 (22%)		28 (25%)	22 (31%)	
10–14 years	57 (31%)	–		15 (33%)	42 (30%)		31 (27%)	26 (36%)	
≥15 years	73 (40%)	–		9 (20%)	64 (46%)[a]		50 (44%)	23 (32%)	
Primary cancer									
Solid tumors	57 (31%)	–		46 (33%)	11 (24%)	0.242	80 (71%)	48 (67%)	0.553
Hematological	128 (69%)	–		93 (67%)	35 (76%)		33 (29%)	24 (33%)	
Treatment									
Operation	70 (38%)	–		14 (30%)	56 (40%)	0.232	40 (35%)	30 (42%)	0.391
Anthracyclines	152 (82%)	–		41 (89%)	111 (80%)	0.154	93 (82%)	59 (82%)	0.951
Alkylating agents	155 (84%)	–		45 (98%)	110 (79%)	0.003	101 (89%)	54 (75%)	0.010
Etoposide	76 (41%)	–		32 (70%)	44 (32%)	<0.001	50 (44%)	26 (36%)	0.273
Radiation	113 (61%)	–		39 (85%)	74 (53%)	<0.001	100%	0%	–
SCT	46 (25%)	–		100%	0%	–	39 (35%)	7 (10%)	<0.001
Recurrence	33 (18%)	–		18 (39%)	15 (11%)	<0.001	28 (25%)	5 (7%)	0.002
Late effects	103 (56%)	–		36 (78%)	67 (48%)	<0.001	77 (68%)	26 (36%)	<0.001
Only 1 late effects	61 (33%)	–		13 (28%)	48 (35%)	0.416	40 (35%)	21 (29%)	0.379
2 or more late effects	42 (23%)	–		23 (50%)	19 (14%)	<0.001	37 (33%)	5 (7%)	<0.001

Age was expressed as mean value ± standard deviation (median value)

CCS childhood cancer survivors, *SCT* stem cell transplantation, *RT* radiation

[a] Adjusted standardized residual ≥+1.96

Table 3 Current social outcome status between each pair groups (i.e., CCS and siblings, CCS with SCT and without SCT, CCS with RT[4] and without RT[4])

	Total CCS ($n = 184$)	Siblings ($n = 72$)	χ^2 (p value) CCS versus siblings	CCS with SCT ($n = 46$)	CCS without SCT ($n = 138$)	χ^2 (p value) SCT versus no SCT	CCS with RT[4] ($n = 112$)	CCS without RT[4] ($n = 72$)	χ^2 (p value) RT versus no RT
Living style									
Living alone	37 (20%)	18 (25%)	0.031	7 (15%)	30 (22%)	0.819	22 (20%)	15 (21%)	0.456
Living with parents	116 (63%)[a]	32 (44%)		31 (67%)	85 (62%)		70 (63%)	46 (64%)	
Living with partner	23 (13%)	18 (25%)[a]		6 (13%)	17 (12%)		13 (12%)	10 (14%)	
Others	8 (4%)	4 (6%)		2 (4%)	6 (4%)		7 (6%)	1 (1%)	
Marital status									
Never married	158 (86%)[a]	54 (75%)	0.090	40 (87%)	118 (86%)	0.844	98 (87%)	60 (86%)	0.444
Married	24 (13%)	17 (24%)[a]		6 (13%)	18 (13%)		15 (13%)	9 (13%)	
Divorced or re-married	1 (0.5%)	1 (1%)		0	1 (1%)		0	1 (1%)	
Marriage rate									
≤24 years of age	2 (2%)	4 (10%)	0.014	0	2 (4%)	0.413	0	2 (4%)	0.112
25–29 years of age	8 (23%)	7 (33%)	0.328	2 (17%)	6 (26%)	0.612	3 (12%)	5 (56%)	0.011
≥30 years of age	14 (56%)	6 (55%)	0.732	4 (100%)	10 (48%)	0.053	12 (63%)	2 (33%)	0.199
Educational achievement									
Lower than high school	7 (4%)	2 (3%)	0.169	0	7 (5%)	0.126	3 (3%)	4 (6%)	0.033
High school	61 (33%)[a]	14 (19%)		14 (30%)	47 (34%)		31 (27%)	30 (42%)[a]	
College/vocational School	51 (28%)	24 (39%)		10 (22%)	41 (30%)		39 (35%)[a]	12 (17%)	
University/graduate school	66 (36%)	32 (45%)		22 (48%)[a]	44 (32%)		40 (35%)	26 (36%)	
Current job									
Student	72 (39%)	24 (33%)	0.011	22 (48%)	50 (36%)	0.694	35 (31%)	37 (51%)[a]	0.099
Company (white collar)	27 (15%)	18 (25%)[a]		5 (11%)	22 (16%)		17 (15%)	10 (14%)	
Part-time job	14 (8%)	8 (11%)		3 (6%)	11 (8%)		12 (11%)[a]	2 (3%)	
Medical job	20 (11%)[a]	0		5 (11%)	15 (11%)		13 (12%)	7 (10%)	
Industry (blue collar)	14 (8%)	3 (4%)		3 (6%)	11 (8%)		11 (10%)	3 (4%)	
Homemaker	15 (8%)	9 (13%)		3 (6)	12 (9%)		9 (8%)	6 (8%)	
Unemployed	7 (4%)	0		3 (6%)	4 (3%)		6 (5%)	1 (1%)	
Others	16 (9%)	10 (14%)		2 (4%)	14 (10%)		10 (9%)	6 (8%)	
Working ability									
No. of days/month	156 (89%)	62 (94%)	0.446	37 (86%)	19 (90%)	0.822	97 (89%)	59 (88%)	0.964
1–2 days/month	13 (7%)	3 (5%)		4 (9%)	9 (7%)		8 (7%)	5 (8%)	
More than 1–2 days/week	7 (4%)	1 (1%)		2 (5%)	5 (4%)		4 (4%)	3 (5%)	

Table 3 continued

	Total CCS ($n = 184$)	Siblings ($n = 72$)	χ^2 (p value) CCS versus siblings	CCS with SCT ($n = 46$)	CCS without SCT ($n = 138$)	χ^2 (p value) SCT versus no SCT	CCS with RT[4] ($n = 112$)	CCS without RT[4] ($n = 72$)	χ^2 (p value) RT versus no RT
Annual income in the last year (JPY)									
<1 million	111 (61%)	40 (58%)	0.586	32 (71%)	79 (58%)	0.276	61 (55%)	50 (70%)[a]	0.098
1–2 million	33 (18%)	9 (13%)		5 (11%)	28 (20%)		27 (24%)[a]	6 (9%)	
2–3 million	21 (12%)	11 (16%)		3 (7%)	18 (13%)		13 (12%)	8 (11%)	
3–5 million	15 (8%)	7 (10%)		5 (11%)	10 (7%)		9 (8%)	6 (9%)	
≥5 million	2 (1%)	2 (3%)		0	2 (2%)		1 (1%)	1 (1%)	

CCS childhood cancer survivors, *JPY* Japanese yen, *SCT* stem cell transplantation, *RT* radiation

[a] Adjusted standardized residual >+1.96

ability or annual income among each group; the CCSs with RT achieved a little lower annual income compared to the CCSs without RT because of a high proportion of students.

The current social outcome status of the CCSs with SCT or RT according to the number of late effects is shown in Table 4. No difference was found with respect to living style, marriage rate and annual income between CCSs lacking any late effects and CCS with only one late effect; however, CCSs with two or more late effects showed extremely low marriage rates (0 and 3%, respectively). A high unemployment rate (from 9 to 5%) was found in CCSs with any late effects in SCT and RT groups.

Figure 1 shows a box plot analysis of the SF-36 subscales and the summary scores among the CCSs with or without SCT and the siblings group. Ceiling effects were found to be high in the PF, RP, BP, SF and RE subscales, for both the CCSs and siblings (supplemental appendix 2). The distributions of each subscale score were much skewed and non-parametric methods using Kruskall–Wallis showed that there was a statistically significant difference in the PF ($p < 0.001$) and GH subscales ($p = 0.001$) between the CCSs with SCT and siblings. A statistically significant difference was also found in the J-PCS and PF subscales between the CCSs with SCT and without SCT, and in the GH subscales between the CCS without SCT and siblings. Figure 2 shows a box plot analysis of the SF-36 subscales and the summary scores among the CCSs with or without RT and the siblings group. A statistically significant difference in the PF ($p = 0.003$) and GH subscales ($p = 0.001$) between the CCSs with SCT and siblings was found. On comparison of the CCSs with the age-matched general population, a statistically significant difference was found in the J-MCS, PF, BP and RE subscales between the CCSs and the nation's standard reference values [25] (supplemental appendix 2).

We created dichotomous variables from each subscale score, to determine whether each subject showed lower SF-36 subscale scores compared to Japan's national norm standards in 2007 [25]. We explored risk factors associated with the lower PF and GH subscale scores of the CCSs, using logistic regression analysis (Table 5). Lower PF scores were associated with recurrence [OR 2.80; 95% confidence interval (CI) 1.04–8.33; $p = 0.041$] and late effects (OR 3.33; 95% CI 1.33–8.33; $p = 0.010$); also, lower GH scores were associated with late effects (OR 2.81; 95% CI 1.35–5.85; $p = 0.006$).

4 Discussion

We found that the long-term social outcome of the CCS group was almost similar to that of siblings in Japan. In line with the Erice statement [28], the majority of survivors

Table 4 Current social outcome status of cancer survivors with or without late effects in the SCT or RT groups

Gender	SCT group ($n = 46$)				RT group ($n = 77$)			
Late effects	Absent ($n = 10$)	Only 1 ($n = 13$)	2 or more ($n = 23$)	χ^2 (p value)	Absent ($n = 36$)	Only 1 ($n = 39$)	2 or more ($n = 36$)	χ^2 (p value)
Living style								
Living alone	0	2 (15%)	5 (22%)	0.126	7 (19%)	8 (21%)	7 (19%)	0.089
Living with parents	6 (60%)	8 (62%)	17 (74%)		18 (50%)	23 (59%)	28 (78%)[a]	
Living with partner	3 (30%)	3 (23%)	0		7 (19%)	6 (15%)	0	
Others	1 (10%)	0	1 (4%)		4 (11%)	2 (5%)	1 (3%)	
Marital status								
Never married	7 (70%)	10 (77%)	23 (100%)[a]	0.028	29 (81%)	33 (82%)	35 (97%)[a]	0.074
Married	3 (30%)	3 (23%)	0		7 (19%)	7 (18%)	1 (3%)	
Educational achievement								
Lower than high school	0	0	0	0.489	1 (3%)	1 (3%)	1 (3%)	0.342
High school	3 (30%)	3 (23%)	8 (35%)		5 (14%)[a]	14 (35%)	12 (33%)	
College/vocational school	1 (10%)	5 (39%)	4 (17%)		17 (47%)	13 (33%)	9 (25%)	
University/graduate school	6 (60%)	6 (39%)	11 (48%)		13 (36%)	12 (30%)	14 (39%)	
Current job								
Student	5 (50%)	3 (23%)[a]	14 (61%)	0.161	10 (28%)	8 (20%)	17 (47%)[a]	0.286
Company (white collar)	2 (20%)	1 (8%)	2 (95)		6 (17%)	7 (18%)	4 (11%)	
Part-time job	0	2 (15%)	1 (4%)		2 (6%)	8 (20%)[a]	2 (6%)	
Medical job	1 (10%)	1 (8%)	3 (13%)		3 (8%)	5 (12%)	5 (14%)	
Industry (blue collar)	0	3 (23%)	0		4 (11%)	5 (12%)	2 (6%)	
Homemaker	1 (10%)	2 (15%)	0		4 (11%)	3 (7%)	2 (6%)	
Unemployed	0	1 (8%)	2 (9%)		1 (3%)	2 (5%)	2 (6%)	
Others	1 (10%)	0	1 (4%)		6 (17%)	2 (5%)	2 (6%)	
Working ability								
No. of days/month	8 (89%)	7 (64%)[a]	22 (96%)	0.082	33 (97%)	32 (84%)	31 (86%)	0.275
1–2 days/month	1 (11%)	2 (18%)	1 (4%)		1 (3%)	3 (8%)	4 (11%)	
More than 1–2 days/week	0	2 (18%)[a]	0		0	3 (8%)	1 (3%)	
Annual income in the last year (JPY[a])								
<1 million	6 (60%)	10 (77%)	16 (73%)	0.247	17 (47%)	22 (56%)	21 (60%)	0.534
1–2 million	1 (10%)	2 (15%)	2 (9%)		11 (31%)	11 (28%)	5 (14%)	
2–3 million	0	0	3 (14%)		4 (11%)	3 (8%)	6 (17%)	
≥3 million	3 (30%)[a]	1 (8%)	1 (5%)		4 (11%)	3 (8%)	3 (9%)	

JPY Japanese yen, *SCT* stem cell transplantation, *RT* radiation

[a] Adjusted standardized residual >+1.96

become relatively well adjusted in adulthood; indeed, there is a proportion exhibiting extraordinary resilience. However, compared to siblings, a significant proportion of CCSs are at an increased risk of developing conditions that require medical, psychological or social care because SCT and RT are closely associated with various late effects reported previously [20, 21]. Our study showed that the marriage rate of the CCSs in 24 years of age or younger patients was a little lower than that of their siblings, and that little difference existed in educational achievement between the CCSs and their siblings [9, 15]. A limitation of our study was that the mean and median ages of the participants were only 23–24 years; this is too young an age to evaluate the total marriage rate, as the average marriage age has been increasing recently (i.e., in 2008, the Japanese national mean age of marriage was 30.2 years for males and 28.5 years for females). By using an analysis of stratification by age, the marriage rate became almost the same in the 25 years or more age group for both females and males.

On the other hand, there were small differences in employment status and annual income among each group

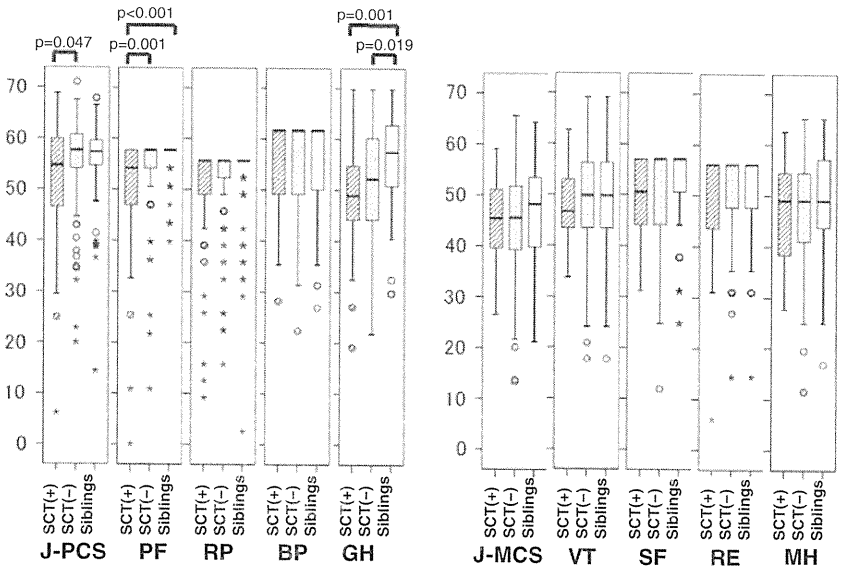

Fig. 1 Box and whisker plot of SF-36 subscale scores according to stem cell transplantation. The *bottom* and *top* of the *box* are the 25th and 75th percentile, respectively, and the thick band near the middle of the box is the 50th percentile (the median). The *ends of the whiskers* represent the lowest datum still within 1.5 interquartile range (IQR) of the lower quartile, and the highest datum still within 1.5 IQR of the upper quartile. The *open circles* are outliers between 1.5 and 3 IQR from the end of a box, and the *asterisks* are extreme values beyond 3 IQR from the end of a box. Kruskal–Wallis test reveal that SF-36 subscales scores of childhood cancer survivors (CCSs) with stem cell transplantation (SCT; *hatched bars*) are significantly lower than those of siblings (*open bars*) in PF and GH subscales, respectively. The J-PCS and PF scores in CCSs with SCT are also significantly lower than those in CCS without SCT (*dotted bars*). The GH scores of CCSs without SCT are significantly lower than those of siblings. All *p* values are adjusted by pairwise multiple comparison

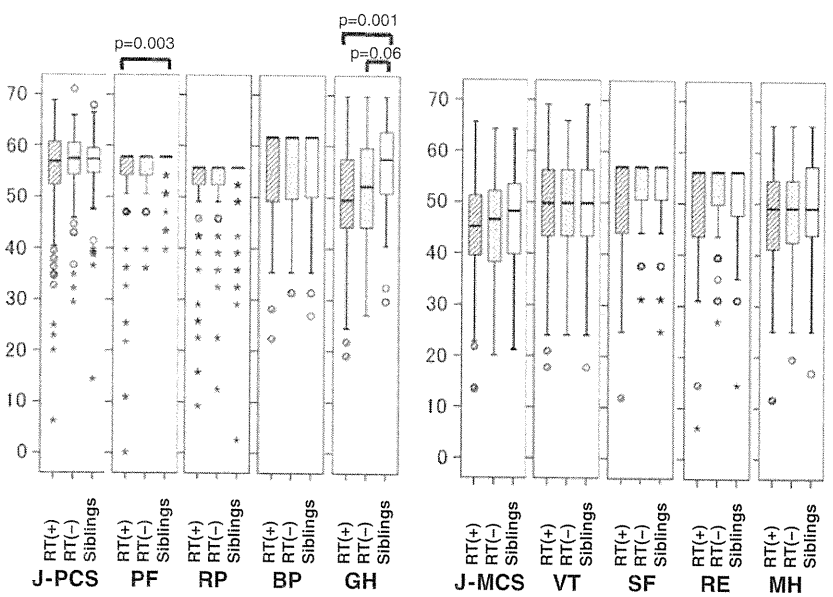

Fig. 2 Box and whisker plot of SF-36 subscale scores according to radiotherapy. Kruskal–Wallis test reveals that SF-36 subscale scores of childhood cancer survivors (CCSs) with radiotherapy (RT; *hatched bars*) are significantly lower than those of siblings (*open bars*) in PF and GH subscales, respectively. The GH scores of CCSs without RT are significantly lower than those of siblings. All *p* values are adjusted by pairwise multiple comparison

in our study despite that both SCT and RT had increased late effects for CCSs [20, 21]. The most important issue was that the proportion of CCSs with two or more late effects who were getting married was quite low. This finding accords with those of previous reports [5, 7]. In our study, the proportion of unemployment tended to be a little high (4%) in the CCSs, especially CCSs with SCT or RT compared to the siblings. A higher unemployment rate (from 9 to 5%) was found in the CCSs with any late effects. The small but significant portion of CCSs experiencing employment difficulties are of great concern [16]; in fact, meta-analysis [16] showed that CCSs were nearly twice as likely to be unemployed than healthy controls (OR 1.85; 95% CI 1.27–2.69) and that survivors in the USA had an overall threefold risk of becoming unemployed, whereas no such risk was found for European survivors. This is very

Table 5 Risk factors associated with lower subscale scores of SF-36 in cancer survivors

Factors	PF scores		χ^2 (p value)	Logistic regression analysis[a]	
	Lower[a] ($n = 51$)	Higher ($n = 132$)		Adjusted odds ratio (95% CI)	p value
Gender (female)	24	83	0.052	0.59 (0.28–1.27)	0.177
Age at Dx (years)					
0–5	13	45	**0.044**	0.40 (0.15–1.09)	0.074
6–10	10	41		0.41 (0.16–1.08)	0.070
≥11	28	46		Ref	
Tx off (years)					
≥15	16	56	0.170	0.88 (0.35–2.22)	0.787
≤14	35	76		Ref	
Solid tumors	23	33	**0.008**	1.85 (0.53–6.46)	0.334
Hematological	28	99		Ref	
Radiation	34	78	0.346	0.72 (0.30–1.73)	0.464
Stem cell transplantation	21	25	**0.002**	1.96 (0.78–4.88)	0.150
Operation	28	40	**0.001**	1.49 (0.45–4.95)	0.513
Recurrence	17	16	**0.001**	**2.80 (1.04–8.33)**	**0.041**
Late effects	41	61	**<0.0001**	**3.33 (1.33–8.33)**	**0.010**
Factors	GH scores		χ^2 (p value)	Logistic regression analysis[a]	
	Lower[a] ($n = 107$)	Higher ($n = 76$)		Adjusted odds ratio (95% CI)	p value
Gender (female)	64	43	0.662	1.48 (0.77–2.87)	0.240
Age at Dx (years)					
0–5	37	21	0.148	1.31 (0.55–3.16)	0.543
6–10	24	27		0.56 (0.26–1.24)	0.155
≥11	46	28		Ref	
Tx off (years)					
≥15	40	32	0.519	0.64 (0.29–1.38)	0.255
≤14	67	44		Ref	
Solid tumors	33	23	0.933	0.65 (0.21–1.96)	0.439
Hematological	74	53		Ref	
Radiation	71	41	0.09	1.10 (0.54–2.23)	0.792
Stem cell transplantation	32	14	0.078	1.11 (0.48–2.60)	0.809
Operation	41	27	0.700	1.26 (0.43–3.63)	0.675
Recurrence	25	8	**0.026**	1.64 (0.60–4.52)	0.335
Late effects	71	31	**0.001**	**2.81 (1.35–5.85)**	**0.006**

[a] After data were presented as T scores with a mean score of 50 and a standard deviation (SD) of 10, T scores were dichotomized, in which a T score below the population score (respective nation's norm matching both age and gender in 2007) classified a respondent as having reported poor HRQOL

important, because the national health-care and social support systems must address these groups of CCSs in Japan. The Children's Cancer Association of Japan (http://www.ccaj-found.or.jp/english/) is now providing assistance and job training to CCSs, and an effective job-training system for CCSs will continue to be warranted in the future.

In our study, the validity and reliability of applying the SF-36 to CCSs in Japan were supported by Cronbach's alpha coefficient. Reulen et al. [13] demonstrated that the occurrence of ceiling effects should be recognized. In our study, a ceiling effect was observed in PF, BP and SF in more than half of the CCSs; it was found to be highest in the RP (66.1%) and RE (61.7%) subscales. These results were quite similar to those pertaining to British CCSS and siblings. The Kruskal–Wallis test showed a statistical significant difference between CCSs with SCT/RT and siblings in the RP and GH subscales. In the CCSS study, the CCSs score was worse than that of siblings with respect to the overall physical ($p < 0.001$), but not the emotional

aspects of HR-QOL. Nonetheless, effect sizes were small, other than in VT [29]. In a Canadian study, three clinical characteristics—having had CNS or bone cancer, more than one treatment series, and two organs dysfunction—were independently associated with poorer QOL in the physical dimensions [14]. Only survivors with two organs with dysfunction reported poorer QOL in both the physical and psychosocial domains. In our study, multivariate analysis-revealed late effects were common risk factors for lower PF and GH subscale scores, neither SCT nor RT were risk factors for lower PF and GH subscale scores after adjusting.

The limitations of our study are as follows: (1) a limited number of subjects were analyzed, (2) patients with solid tumors were underrepresented, compared to those with hematological cancers, (3) a selection bias may have been presented, because patients were not recruited through random sampling and (4) some patients' siblings were inappropriate as controls because they experienced significant psychosocial distress during the patients' cancer experience. Nonetheless, our report fills a gap in the published literature—and usefully so, given the numerous articles in Japan that survey social outcomes and QOL of young adult CCSs.

5 Conclusions

Our study revealed that the long-term social outcome of the CCS group was almost similar to that of the control (i.e., their siblings), but a significant proportion of CCSs were at an increased risk of developing poor social outcomes and QOL, thus requiring psychological or social care if they had some late effects.

Acknowledgments The institutions that provided patient data and recruited CCSs to the survey are listed in the supplemental appendix 1. This study was supported by research grants from the Japanese Ministry of Health, Labor, and Welfare ["Study of quality of life and prognosis in childhood cancer survivors and establishment of the long-term follow-up system (Principal investigator: Yasushi Ishida)" and "Study to establish the standard treatment for childhood hematological malignancies (Principal investigator: Keizo Horibe)"].

References

1. Schwartz C, Hobbie W, Constine L, Ruccione K, editors. Survivors of childhood and adolescent cancer. Berlin: Springer; 2005.
2. Wallace H, Green D, editors. Late effects of childhood cancer. London: Arnold; 2004.
3. Oeffinger KC, Mertens AC, Sklar CA, Kawashima T, Hudson MM, Meadows AT, et al. Chronic health conditions in adult survivors of childhood cancer. N Engl J Med. 2006;355(15):1572–82. doi:10.1056/NEJMsa060185.
4. Boman KK, Lindblad F, Hjern A. Long-term outcomes of childhood cancer survivors in Sweden: a population-based study of education, employment, and income. Cancer. 2010;116(5):1385–91. doi:10.1002/cncr.24840.
5. Gurney JG, Krull KR, Kadan-Lottick N, Nicholson HS, Nathan PC, Zebrack B, et al. Social outcomes in the Childhood Cancer Survivor Study cohort. J Clin Oncol. 2009;27(14):2390–5. doi:10.1200/JCO.2008.21.1458.
6. Johannsdottir IM, Hjermstad MJ, Moum T, Wesenberg F, Hjorth L, Schroder H, et al. Social outcomes in young adult survivors of low incidence childhood cancers. J Cancer Surviv. 2010. doi:10.1007/s11764-009-0112-3.
7. Janson C, Leisenring W, Cox C, Termuhlen AM, Mertens AC, Whitton JA, et al. Predictors of marriage and divorce in adult survivors of childhood cancers: a report from the Childhood Cancer Survivor Study. Cancer Epidemiol Biomarkers Prev. 2009;18(10):2626–35. doi:10.1158/1055-9965.EPI-08-0959.
8. Dama E, Maule MM, Mosso ML, Alessi D, Ghisleni M, Pivetta E, et al. Life after childhood cancer: marriage and offspring in adult long-term survivors—a population-based study in the Piedmont region, Italy. Eur J Cancer Prev. 2009. doi:10.1097/CEJ.0b013e3283307770.
9. Lancashire ER, Frobisher C, Reulen RC, Winter DL, Glaser A, Hawkins MM. Educational attainment among adult survivors of childhood cancer in Great Britain: a population-based cohort study. J Natl Cancer Inst. 2010;102(4):254–70. doi:10.1093/jnci/djp498.
10. Mulrooney DA, Dover DC, Li S, Yasui Y, Ness KK, Mertens AC, et al. Twenty years of follow-up among survivors of childhood and young adult acute myeloid leukemia: a report from the Childhood Cancer Survivor Study. Cancer. 2008;112(9):2071–9. doi:10.1002/cncr.23405.
11. Mody R, Li S, Dover DC, Sallan S, Leisenring W, Oeffinger KC, et al. Twenty-five-year follow-up among survivors of childhood acute lymphoblastic leukemia: a report from the Childhood Cancer Survivor Study. Blood. 2008;111(12):5515–23. doi:10.1182/blood-2007-10-117150.
12. Frobisher C, Lancashire ER, Winter DL, Jenkinson HC, Hawkins MM. Long-term population-based marriage rates among adult survivors of childhood cancer in Britain. Int J Cancer. 2007;121(4):846–55. doi:10.1002/ijc.22742.
13. Reulen RC, Zeegers MP, Jenkinson C, Lancashire ER, Winter DL, Jenney ME, et al. The use of the SF-36 questionnaire in adult survivors of childhood cancer: evaluation of data quality, score reliability, and scaling assumptions. Health Qual Life Outcomes. 2006;4:77. doi:10.1186/1477-7525-4-77.
14. Maunsell E, Pogany L, Barrera M, Shaw AK, Speechley KN. Quality of life among long-term adolescent and adult survivors of childhood cancer. J Clin Oncol. 2006;24(16):2527–35. doi:10.1200/JCO.2005.03.9297.
15. Servitzoglou M, Papadatou D, Tsiantis I, Vasilatou-Kosmidis H. Quality of life of adolescent and young adult survivors of childhood cancer. J Pediatr Nurs. 2009;24(5):415–22. doi:10.1016/j.pedn.2007.02.073.
16. de Boer AG, Verbeek JH, van Dijk FJ. Adult survivors of childhood cancer and unemployment: a metaanalysis. Cancer. 2006;107(1):1–11. doi:10.1002/cncr.21974.
17. McDougall J, Tsonis M. Quality of life in survivors of childhood cancer: a systematic review of the literature (2001–2008). Support Care Cancer. 2009;17(10):1231–46. doi:10.1007/s00520-009-0660-0.
18. Wakefield CE, McLoone J, Goodenough B, Lenthen K, Cairns DR, Cohn RJ. The psychosocial impact of completing childhood

cancer treatment: a systematic review of the literature. J Pediatr Psychol. 2010;35(3):262–74. doi:10.1093/jpepsy/jsp056.
19. Reulen RC, Winter DL, Lancashire ER, Zeegers MP, Jenney ME, Walters SJ, et al. Health-status of adult survivors of childhood cancer: a large-scale population-based study from the British Childhood Cancer Survivor Study. Int J Cancer. 2007;121(3): 633–40. doi:10.1002/ijc.22658.
20. Ishida Y, Honda M, Ozono S, Okamura J, Asami K, Maeda N, et al. Late effects and quality of life of childhood cancer survivors: part 1. Impact of stem cell transplantation. Int J Hematol. 2010;91(5):865–76. doi:10.1007/s12185-010-0584-y.
21. Ishida Y, Sakamoto N, Kamibeppu K, Kakee N, Iwai T, Ozono S, et al. Late effects and quality of life of childhood cancer survivors: part 2. Impact of radiotherapy. Int J Hematol. 2010;92(1): 95–104. doi:10.1007/s12185-010-0611-z.
22. Kamibeppu K, Sato I, Honda M, Ozono S, Sakamoto N, Iwai T, et al. Mental health among young adult survivors of childhood cancer and their siblings including posttraumatic growth. J Cancer Surviv. 2010. doi:10.1007/s11764-010-0124-z.
23. Ishida Y, Honda M, Kamibeppu K, Ozono S, Iwai T, Kakee N, et al. Cross-sectional survey on the late effects and QOL of childhood cancer survivors: part 1. J Jpn Pediatr Soc. 2010; 114(4):665–75 (Japanese).
24. Fukuhara S, Bito S, Green J, Hsiao A, Kurokawa K. Translation, adaptation, and validation of the SF-36 Health Survey for use in Japan. J Clin Epidemiol. 1998;51(11):1037–44. S0895-4356(98) 00095-X [pii].
25. Fukuhara S, Suzukamo Y. Manual of SF-36v2 Japanese version. Kyoto: Institute for Health Outcomes and Process Evaluation Research; 2009.
26. Fukuhara S, Ware JE Jr, Kosinski M, Wada S, Gandek B. Psychometric and clinical tests of validity of the Japanese SF-36 Health Survey. J Clin Epidemiol. 1998;51(11):1045–53. S0895-4356(98)00096-1 [pii].
27. Norušis M. PASW statistics 18 guide to data analysis. NJ: Prentice Hall; 2010.
28. Haupt R, Spinetta JJ, Ban I, Barr RD, Beck JD, Byrne J, et al. Long term survivors of childhood cancer: cure and care. The Erice statement. Eur J Cancer. 2007;43(12):1778–80. doi: 10.1016/j.ejca.2007.04.015.
29. Zeltzer LK, Lu Q, Leisenring W, Tsao JC, Recklitis C, Armstrong G, et al. Psychosocial outcomes and health-related quality of life in adult childhood cancer survivors: a report from the childhood cancer survivor study. Cancer Epidemiol Biomarkers Prev. 2008;17(2):435–46. doi:10.1158/1055-9965.EPI-07-2541.

PEDIATRICS INTERNATIONAL Official Journal of the Japan Pediatric Society
Pediatrics International (2011) **53**, 291–299 doi: 10.1111/j.1442-200X.2010.03293.x

Original Article

Medical visits of childhood cancer survivors in Japan: A cross-sectional survey

Yasushi Ishida,[1]* Shuichi Ozono,[5] Naoko Maeda,[7] Jun Okamura,[6] Keiko Asami,[8] Tsuyako Iwai,[9] Kiyoko Kamibeppu,[2] Naoko Sakamoto,[3] Naoko Kakee[4] and Keizo Horibe[7]

[1]*Department of Pediatrics, St. Luke's International Hospital,* [2]*Department of Family Nursing, The University of Tokyo, and Departments of* [3]*Epidemiology, and* [4]*Health Policy, National Research Institute for Child Health and Development, Tokyo,* [5]*Department of Pediatrics, Kurume University School of Medicine,* [6]*Institute for Clinical Research, National Kyusyu Cancer Center, Fukuoka,* [7]*Department of Pediatrics and Clinical Research Center, Nagoya Medical Center, Aichi,* [8]*Department of Pediatrics, Niigata Cancer Center Hospital, Niigata, and* [9]*Department of Hemato-oncology, Kagawa Children's Hospital, Kagawa, Japan*

Abstract ***Background***: Although more children with cancer continue to be cured, these survivors experience various late effects. Details of the medical visit behaviors of childhood cancer survivors (CCS) in adulthood remain to be elucidated.

Methods: In order to examine medical visits in the past and future of CCS, we performed a cross-sectional survey with self-rating questionnaires on medical visits of CCS compared with control groups (their siblings and the general population).

Results: Questionnaires were completed by 185 CCS, 72 of their siblings and 1000 subjects from the general population and the results were analyzed. Mean ages at this survey and the duration after therapy completions of CCS were 23 and 12 years, respectively. We found that the previous treatment hospitals (where CCS were treated for their cancer) were the most commonly visited medical facilities for the CCS group (74% for female patients and 64% for male patients) and more than half of the CCS preferred to continue visiting the previous treatment hospital with enough satisfaction in Japan. The multivariate analysis showed that female sex and relapse were significantly associated with the past visits to the previous treatment hospital and that the CCS with brain tumors or bone/soft tissue sarcomas and CCS with any late effects tended to continue the relationships with the hospital. In addition female sex was also significantly associated with desired future visits to the previous treatment hospital. On the other hand, the married CCS tended to be disinclined to visit the hospital it in the future.

Conclusions: In order to optimize risk-based care and promote health for CCS after adulthood, we should discuss the medical transition with CCS and their parents.

Key words childhood cancer survivors, cross-sectional survey, health care, medical visit, transition.

As a result of advances in treatment, 70–80% of children who receive a diagnosis of cancer become long-term survivors. In Japan, the estimated number of childhood cancer survivors (CCS) is >50 000, or approximately 1 in 700 adults between 20 and 39 years. Although more children with cancer continue to be cured, these survivors experience various health problems or late effects from treatment, such as organ dysfunction, physical disabilities, reproductive problems, cognitive impairments, and an increased risk for developing secondary cancers.[1,2] Oeffinger *et al.*[3] reported that 62.3% of CCS exhibit at least one late effect and 27.5% exhibit two or more late effects. Our previous reports[4,5] also showed similar trends that late effects were observed in 50% of female CCS and 63% of male CCS. Because chronic conditions are common in CCS,[3] they need a continuous and comprehensive medical follow up after adulthood.

The details of the medical visit behaviors of CCS in adulthood remain to be elucidated. The Childhood Cancer Survivors Study (CCSS) demonstrated that less than 50% of CCS had a cancer-related visit and less than 20% of CCS had a visit at a cancer center after 15 years after the diagnosis.[6] Despite the low proportion of survivor-focused and risk-based care in North America, 87% of young adult CCS have a primary care or family physician in charge.[7] As the relationships between the attending pediatric oncologists or surgeons and CCS/their parents seem to be very intimate in Japan, their medical visit behaviors might be different from those in Western countries. We investigated the medical

Correspondence: Yasushi Ishida, MD, Department of Pediatrics, St. Luke's International Hospital, 10-1 Akashi-cho, Chuo-ku, Tokyo, 104-0044 Japan. Email: yaishida@luke.or.jp

*Previous address: Ehime University Graduate School of Medicine, Department of Pediatrics, Toon, Japan

Received 28 June 2010; revised 10 September 2010; accepted 21 September 2010.

visit behaviors of young adult CCS and compared them with their siblings and the general population in Japan.

Methods

Study design

We performed a cross-sectional survey with self-rating questionnaires on medical visits of childhood cancer survivors compared with control groups (their siblings and the general population).[8] We simultaneously obtained medical data on the CCS from their attending pediatric oncologists or surgeons. The study was conducted from 1 August 2007 to 31 March 2009.

Participants and methods

The CCS and their siblings were recruited from the participating hospitals listed in the Appendix. The eligibility criteria for CCS were as follows: (i) the subjects were ≥16 years old at the time of survey; (ii) they were diagnosed as CCS at ≤18 years of age and >5 years had passed since the diagnosis of cancer; (iii) the subjects had continued in remission for >1 year without additional need for anticancer therapy; (iv) the subjects were informed about the diagnosis; and (v) informed consent was provided by CCS and their guardians. The criteria for subjects to be excluded from the survey were as follows: (i) the attending physicians believed that the survey would cause an undesirable effect on the CCS; (ii) the subjects had some underlying disease beside cancer, which affected their social outcome or quality of life; or (iii) the subjects were unable to answer the questionnaires by themselves. The general population was recruited by the Web-based research consulting company (Cross Marketing, Tokyo, Japan). The participants from the general population were selected by confirming that he or she neither had a childhood cancer experience nor a sibling with childhood cancer.

With the informed consent of the CCS or their siblings and their guardian, the attending pediatric oncologists or surgeons distributed questionnaires and asked the subjects to return them to the principal investigator (Y.I.) by mail anonymously within 1 month. On recruiting the general population group, the researcher contracted the role out to a cross-marketing organization that provides online research with Web-based methods using the same questionnaires for the research panel. The general population participants were matched with the CCS group in age, sex, living area, and job status.

Measurement of variables

Patient records were reviewed to obtain information about cancer-related variables, including diagnosis, birth year and month, age at diagnosis, age at therapy completion, treatment, and late effects of CCS. Late effects were defined as adverse events, which were grade 2 (symptomatic or needing some intervention) or higher using the Common Terminology Criteria for Adverse Events, Version 3 (CTCAEv3), originally developed by the National Cancer Institute (Japanese CTCAE v.3.0 by JCOG and JSCO, http://www.jcog.jp/). We classified the late effects into 14 categories: cardiovascular dysfunction, pulmonary dysfunction, endocrine dysfunction, short stature, kidney and bladder dysfunction, bone or muscle problems, skin problems or hair loss, neurocognitive impairment, gastrointestinal dysfunction, liver dysfunction, immunological dysfunction, secondary cancers, chronic infection, and others. Maintaining the confidentiality of medical information respects patients' privacy, so we used an encrypted number to send the data to the principal investigator.

We estimated the prevalence of outcomes among CCS and the control groups (their siblings and the general population). There are a total of 220 items in the questionnaire with three items for free writing. In this article we focused on the medical visiting items according to sex. It contains nine items: regular physical screening, visited clinics or hospitals during last 1 year, frequency of medical visits, reasons for medical visit, satisfaction with the visited clinics or hospitals, treatment summary, desired clinics or hospital to visit in future. Medical facilities were classified into nine categories: previous treatment hospital, hospital specialist, pediatric clinic, internal medicine clinic, long-term follow-up clinic, psychiatrist or psychologist, Oriental medicine, alternative medicine, and others. Previous treatment hospital was defined as the hospital where CCS were treated for their cancer during childhood. Hospital specialist was defined as the internal specialist in the same or different hospital as when the CSS received cancer treatment. The reasons for medical visit cited by them were classified into nine categories: annual routine check, childhood primary disease-related, common diseases (such as the common cold), complication-related, late-effects-associated, general health care, consultation for school or marriage, vaccination and others.

Ethical issues

The study was performed in accordance with the Declaration of Helsinki, and was approved by the ethics committee of the principal investigator's institution (Y. Ishida, Ehime University Graduate School of Medicine and St. Luke's International Hospital). The study was also approved by the local ethics committees of all the participating hospitals before initiation.

Statistical analysis

We performed χ^2-tests or Fisher's exact test (for any cells with expected counts <5) within categorical predictors, and the *t*-test or ANOVA for continuous variables. Adjusted odds ratios (OR) for target outcomes were estimated with the use of logistic regression analysis. To avoid multicollinearity, a pair-wise assessment of associations between predictors was examined. Data were analyzed with SPSS ver. 18.0 (IBM SPSS Japan, Tokyo, Japan).

Results

The demographic data of the participants are shown in Table 1. A total of 189 CCS (72% response rate) returned questionnaires but four CCS were excluded due to the following: two CCS had underlying disease besides cancer, which affected their quality of life; one questionnaire was written by the CCS's mother; and one CCS was 20 years of age at diagnosis. Also, we excluded two questionnaires from CCS siblings because two siblings were 14

Table 1 Demographic data of the participants

Group	Female			ANOVA or χ^2 (P-value)	Male			ANOVA or χ^2 (P-value)
	CCS (n = 108)	Siblings (n = 42)	General (n = 584)		CCS (n = 77)	Siblings (n = 30)	General (n = 416)	
Sex	58.4%	58.3%	58.4%	1.000	41.6%	42.7%	41.6%	1.000
Age at diagnosis	8.32 ± 4.8 (8.0)	10.1 ± 6.2 (9.0)	–	**<0.001**	8.53 ± 5.0 (8.0)	11.6 ± 4.1 (12.0)	–	**<0.001**
Age at survey	23.2 ± 4.9 (23)	25.6 ± 5.5 (24)	23.9 ± 5.4 (23)	**0.045***	23.1 ± 5.1 (22)	24.3 ± 4.6 (24)	23.8 ± 5.6 (23)	0.504
16–19 years of age	28 (26%)	3 (7%)	146 (25%)	0.285	19 (25%)	4 (13%)	102 (25%)	0.407
20–24 years of age	41 (38%)	20 (48%)	228 (39%)		34 (44%)	12 (40%)	187 (45%)	
25–29 years of age	25 (23%)	11 (26%)	134 (23%)		13 (17%)	10 (33%)	69 (17%)	
≥30 years of age	14 (13%)	8 (19%)	76 (13%)		11 (14%)	4 (13%)	58 (14%)	
Living area								
Kyusyu-Okinawa	33 (31%)	6 (14%)	173 (30%)	0.310	15 (20%)	2 (7%)	80 (19%)	0.514
Chu-Shikoku	24 (22%)	15 (36%)	131 (22%)		28 (36%)	9 (30%)	155 (37%)	
Kinki-Chubu	15 (14%)	9 (21%)	87 (15%)		10 (13%)	5 (17%)	52 (13%)	
Kantou-Koushin-Etsu	27 (25%)	11 (26%)	144 (25%)		22 (29%)	14 (47%)	118 (28%)	
Touhoku-Hokkaido	9 (8%)	1 (2%)	49 (8%)		2 (3%)	0	11 (3%)	
Work status								
Student	38 (35%)	13 (31%)	205 (35%)	0.140	29 (38%)	11 (37%)	173 (42%)	0.193
Part-time	15 (14%)	5 (12%)	58 (10%)		7 (9%)	4 (13%)	41 (10%)	
Full-time	36 (33%)	11 (26%)	230 (39%)		26 (34%)	15 (50%)	146 (35%)	
Others	19 (18%)	13 (31%)	91 (16%)		15 (20%)	0	56 (14%)	
Primary cancer								
Hematological	77 (71%)	NA	NA		51 (66%)	NA	NA	
Brain tumor	4 (4%)	NA	NA		6 (8%)	NA	NA	
Bone or soft tissue sarcoma	9 (8%)	NA	NA		9 (12%)	NA	NA	
Other solid tumor	18 (17%)	NA	NA		11 (14%)	NA	NA	
Treatment								
Multi-agents chemotherapy	105 (97%)	NA	NA		77 (100%)	NA	NA	
Radiation	68 (63%)	NA	NA		45 (58%)	NA	NA	
Stem cell transplantation	27 (25%)	NA	NA		19 (25%)	NA	NA	
Operation	34 (32%)	NA	NA		36 (47%)	NA	NA	
Recurrence	17 (16%)	NA	NA		16 (21%)	NA	NA	
Any late effects	54 (50%)	NA	NA		49 (64%)	NA	NA	

*Female CCS vs female siblings: $P = 0.035$ (Turkey) and 0.025 (Dunnett). Age was expressed as mean value ± SD (median value). CCS, childhood cancer survivors; NA, not available.

and 15 years of age at the time of survey, respectively. Mean ages at diagnosis were 8.3 years for female CCS and 8.5 years for male CCS. We conducted this survey at a mean age of 23.2 years for female and 23.1 years for male CSS. In regards to primary cancers, acute lymphoblastic leukemia comprised 44% of CCS, followed by acute myeloid leukemia/myelodysplastic syndrome, and lymphoma. Seventy percent of primary cancers were hematological. As for the treatment of the primary cancer, 98% of CCS received multi-agent chemotherapy, 61% radiation, 38% surgery, and 25% hematopoietic stem cell transplantation. Among CCS, one or more late effects were found in 56%, two or more late effects in 17% and three or more in 9%, respectively. Frequent late effects included endocrine dysfunction (21%), short stature (14%), bone/soft tissue damage (10%), liver dysfunction (9%), and skin disorder/hair loss (7%) (shown in the previous reports[4,5]).

Table 2 shows the clinical medical visits during the previous year. Both female and male CCS attended significantly more regular health screenings and regular medical visits than the control groups. Ninety-five percent of the CCS group visited some medical facilities during the previous year but only 29% of them knew about and had a treatment summary. One-third of CCS were not aware of the presence of the treatment summary. The previous treatment hospitals were the most commonly visited medical facilities for the CCS group (74% for female and 64% for male CCS). Internal medicine clinics (primary care physicians) were twice more common for the control groups compared to the CCS group. No difference was shown for frequency of medical visits among the three groups. Among the reasons given for visiting the hospital, all three groups had common problems, such as simple upper respiratory infection, vaccination and health care, however, only CCS had an annual routine health check, cancer-related, and complication- and late-effects-related visits.

Subjects who answered that they visited the outpatient medical facility during the previous year were questioned about their satisfaction with it. More CCS answered that they were satisfied with the present medical facilities than the control groups (Fig. 1). Among 126 CCS who visited the previous treatment hospital in the previous year, 107 (85%) CCS answered that it met their needs of a clinical visit, whereas 38 (70%) out of 54 who visited the internal medicine specialists, 25 (71%) out of 35 who visited the primary care physicians, and 19 (73%) out of 26 who visited the long-term follow-up clinic answered that it met their needs of a clinical visit. Figure 2 shows the most desired medical facility to visit in the future. Two-thirds of the CCS selected the previous treatment hospitals followed by the long-term follow-up clinic (26% of CCS). On the other hand, the internal medicine specialists followed by primary care physicians were significantly predominant in their siblings and the general population group.

We explored the factors associated with the CCS who visited the previous treatment hospital in the past and the future (Table 3). The univariate analysis showed that the CCS with any late effects, relapse and those unmarried visited the previous treatment hospital in the last year frequently and that the married CCS were disinclined to visit the previous treatment hospital in the future. The multivariate analysis showed that female sex and relapse were significantly associated with the past visits. Considering the high OR, the patients with brain tumors or bone/soft tissue sarcomas and CCS with any late effects tended to continue the relationships with the previous treatment hospital both in the past and the future. In addition, female sex was also significantly associated with the future visit to the previous treatment hospital, and the married CCS tended to be disinclined to visit the previous treatment hospital in the future. The CCS with longer duration after therapy completion had not visited the previous treatment hospital in the past (OR < 1.0) but wanted to do so in the future (OR > 1.0).

Discussion

We found that the previous treatment hospitals were the most commonly visited medical facilities for the CCS group and more than half of CCS preferred to continue to visit the previous treatment hospital with enough satisfaction even in young adulthood (23 ± 5, median 23 years of age). It is understandable that the CCS with brain tumors or bone/soft tissue sarcomas tended to continue the relationships with the previous treatment hospitals, because generally neurosurgeons and orthopedic surgeons are conducting clinical practices for all age patients in our country and CCS with brain tumors or bone/soft tissue sarcomas often need the care of specialists. We also found that female sex was associated with both past and future visits to the previous treatment hospital, which is compatible with the findings of Cox's report.[9]

Our results contrast with the results of CCSS.[6,10] Oeffinger *et al.*[6] reported that primary care physicians provide health care for most young adult CCS at a mean age of 26.8 years. They showed that 87% reported general medical contact, 71% a general physical examination, 42% a cancer-related visit, and 19%, a visit at a cancer center. But Hispanic CCS were more likely to report a cancer center visit (women: OR, 1.5; men: OR, 1.7).[11] Despite the high percentage of general medical contact, it is a problem that the majority of CCS do not receive recommended risk-based care.[7,10] In Western countries, risk-based health care for CCS has been promoted by nurse practitioners and/or primary care physicians (or general practitioners) recently.[12]

In our study, many CCS have received regular health examinations by the previous treatment hospitals during young adulthood as expected. This is a double-edged sword, because many CCS have continued to visit their previous treatment hospital well after completion of their treatment and through adulthood; many CCS often quit regular medical visits after their attending pediatrician's transfer or retirement. This is one of the main reasons of follow-up loss for CCS in Japan primarily because bonding between CCS and pediatricians might be strong, but also because special long-term follow-up clinics have not been widely established in Japan. To prevent this type of follow-up loss, CCS and their families should be fully informed of the importance of long-term follow up. After completion of treatment for the original cancer, we should provide the CCS and their parents with a

Table 2 Clinical medical visits during previous year

Gender	Female			χ^2 or Fisher's exact test (P-value)	Male			χ^2 or Fisher's exact test (P-value)
Group	CCS (n = 107)	Siblings (n = 42)	General (n = 584)		CCS (n = 77)	Siblings (n = 30)	General (n = 416)	
Regular health screening	82 (77%)	24 (57%)	302 (52%)	<0.0001	61 (79%)	20 (67%)	191 (46%)	<0.0001
Regular medical visit	77 (72%)	4 (10%)	59 (10%)	<0.0001	52 (68%)	2 (7%)	32 (8%)	<0.0001
Do you have a treatment summary?								
Know and have	29 (27%)	NA	NA	–	24 (31%)	NA	NA	–
Know but do not have	46 (43%)	NA	NA	–	26 (34%)	NA	NA	–
Do not know	32 (30%)	NA	NA	–	27 (35%)	NA	NA	–
Did you visit any medical facilities in the previous year?								
Yes	104 (97%)	36 (86%)	328 (56%)	<0.0001	71 (92%)	21 (70%)	152 (37%)	<0.0001
If yes, what kind of medical facility did you visit? (Count all)								
Previous treatment hospital	77 (74%)	2 (6%)	13 (4%)	<0.0001	49 (64%)	0	11 (7%)	<0.0001
Hospital specialist	27 (26%)	11 (31%)	99 (30%)	0.701	28 (36%)	8 (38%)	45 (30%)	0.308
Pediatric clinic	11 (11%)	0	11 (3%)	0.004	3 (4%)	0	4 (3%)	0.563
Internal medicine clinic	21 (20%)	15 (42%)	162 (49%)	0.0011	15 (21%)	8 (38%)	72 (47%)	<0.0001
Long-term follow-up clinic	17 (16%)	0	0	<0.0001	9 (13%)	0	0	<0.0001
Mental health clinic	1 (1%)	2 (6%)	36 (11%)	0.005	6 (9%)	0	11 (7%)	0.400
Oriental (*kanpo*) medicine	2 (2%)	0	11 (3%)	0.425	1 (1%)	1 (5%)	2 (1%)	0.499
Alternative medicine	17 (16%)	7 (19%)	34 (10%)	0.112	6 (9%)	2 (10%)	10 (7%)	0.817
Others	11 (11%)	7 (19%)	62 (19%)	0.134	5 (7%)	4 (19%)	24 (16%)	0.152
Frequency of clinic visits								
Once/year	15 (14%)	3 (8%)	41 (13%)	0.452	13 (18%)	7 (29%)	34 (22%)	0.421
2–3 times/year	31 (30%)	17 (47%)	126 (38%)		25 (35%)	8 (33%)	63 (41%)	
4–5 times/year	29 (28%)	9 (25%)	75 (23%)		14 (19%)	7 (29%)	31 (20%)	
6–10 times/year	13 (13%)	1 (3%)	27 (8%)		7 (10%)	1 (4%)	9 (6%)	
>10 times/year	16 (15%)	6 (17%)	59 (18%)		13 (18%)	1 (4%)	15 (10%)	
If you visited a medical facility last year, what was the purpose of your visit? (Count all)								
Annual routine check	75 (74%)	10 (29%)	84 (26%)	<0.0001	50 (71%)	7 (35%)	42 (28%)	<0.0001
Primary disease-related	9 (9%)	1 (3%)	2 (0.6%)	<0.0001	6 (9%)	0	2 (1%)	0.014
Common urgent care-related	39 (39%)	17 (50%)	164 (50%)	0.128	25 (36%)	10 (50%)	58 (38%)	0.508
Complication-related	7 (7%)	0	1 (0.3%)	<0.0001	5 (7%)	1 (5%)	0	0.005
Late-effects-associated	11 (11%)	0	0	<0.0001	3 (4%)	0	0	0.025
General health care	23 (22%)	7 (2%)	65 (20%)	0.859	17 (24%)	4 (20%)	26 (17%)	0.483
Consultation (school/marriage)	1 (1%)	2 (6%)	4 (1%)	0.093	1 (1%)	0	2 (1%)	0.871
Vaccination	34 (34%)	6 (18%)	85 (26%)	0.137	18 (26%)	4 (20%)	30 (20%)	0.593
Others	11 (11%)	5 (15%)	24 (7%)	0.233	5 (7%)	3 (15%)	9 (6%)	0.326

CCS, childhood cancer survivors; NA, not available.

Table 3 Clinical characteristics of childhood cancer survivors who visited or want to visit their previous treatment hospital

	Have visited the previous treatment hospital in last 1 year					Want to visit the previous treatment hospital in the future				
	Yes (n = 125)	No (n = 57)	χ^2 or Fisher's exact test (P-value)	Adjusted odds ratio (95% CI)	P-value	Yes (n = 94)	No (n = 54)	χ^2 or Fisher's exact test (P-value)	Adjusted odds ratio (95% CI)	P-value
Age at survey										
16–19 years of age	32	14	0.260			24	11	0.481		
20–24 years of age	55	20				37	24			
25–29 years of age	25	11				22	9			
≥30 years of age	13	12				11	10			
Sex: Female	77	29	0.174	**2.67 (1.27–5.62)**	**0.010**	60	27	0.100	**2.24 (1.05–4.78)**	**0.036**
Years after treatment completion										
0–9 years	44	11	0.065	Ref		29	18		Ref	
10–14 years	38	18		0.64 (0.24–1.73)	0.381	31	17		**1.41 (0.56–3.56)**	0.467
More than 14 years	43	28		0.66 (0.23–1.87)	0.435	34	19		**1.98 (0.68–5.71)**	0.208
Primary cancer										
Hematological cancer	85	41	0.053	Ref		69	39	0.643	Ref	
Brain tumor	9	1		**6.55 (0.62–69.1)**	0.118	6	2		**2.37 (0.40–13.9)**	0.339
Bone or soft tissue sarcoma	15	2		**3.99 (0.74–21.5)**	0.107	8	4		**2.13 (0.52–8.68)**	0.291
Other solid tumor	16	13		0.54 (0.20–1.45)	0.222	11	10		0.61 (0.21–1.79)	0.370
Any late effects	77	24	0.014	**2.05 (0.92–4.57)**	0.078	48	30	0.598	0.77 (0.34–1.76)	0.537
Relapse	29	4	0.009	**4.04 (1.17–14.0)**	**0.028**	18	9	0.707	1.38 (0.49–3.88)	0.541
Treatment										
Surgery	46	22	0.816			35	18	0.634		
Radiation	79	32	0.365			57	35	0.614		
Stem cell transplantation	34	12	0.376			26	12	0.466		
Social Factors										
Married	12	12	0.026	0.42 (0.15–1.20)	0.105	9	12	0.036	**0.34 (0.11–1.76)**	**0.054**
Student	57	19	0.091	1.81 (0.78–4.25)	0.170	40	20	0.413	1.52 (0.64–3.63)	0.341
Full-time job	43	19	0.922			35	17	0.530		
Annual income ≥ ¥2million	23	13	0.501			17	10	0.954		
Medical visits >3 times/year	64	25	0.308			44	34	0.077	0.56 (0.27–1.19)	0.561
Education > high school	77	39	0.375			66	32	0.175		
Treatment summary										
Know and have	37	16	0.774			34	13	0.223		
Know but do not have	47	25				34	24			
Do not know	41	17				25	19			

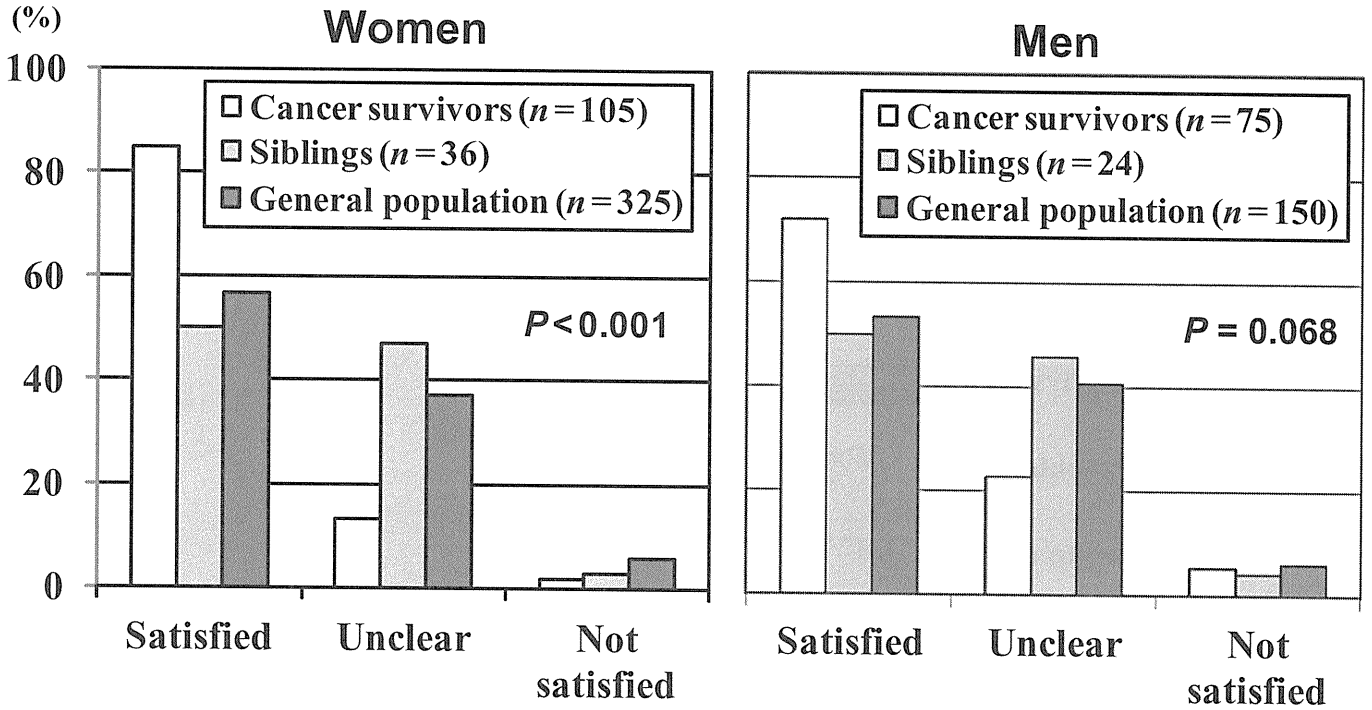

Fig. 1 Satisfaction for the outpatient medical facility. This question was limited to the subjects who went to the outpatient medical facility during the previous year. The childhood cancer survivors answered that they were more satisfied with the present outpatient medical facilities (85% for women and 71% for men) than their siblings (50% for both women and men) and the general population (56% for women and 53% for men).

treatment summary with suggestions on the type and timing of the follow-up evaluations to monitor the possible late effects.[13] In this survey, however, only 29% of them knew and had a treatment summary and there was no association between having the treatment summary and favor of visiting the previous treatment hospital. It doesn't suggest that CCS with information about the importance of long-term follow up want to visit the previous treatment hospital continuously.

The Erice statement[14] says, "when the survivor enters adulthood, he/she should be referred to an appropriate health care provider who coordinates long term care. If any specific problem arises that might be considered a possible late effect of treatments received during childhood, the survivor should be referred to an appropriate specialist." The fundamental purposes underlying health care transition from the pediatric to adult setting for young adult CCS are to optimize risk-based care and promote health for CCS after adulthood.[15,16] Care by pediatricians alone might be not enough to support the adult-oriented healthcare and prevention of lifestyle-related diseases in adulthood.[15] In our study, the preference to continue to visit the previous treatment hospital in future by more than half of the CCS might show that they don't understand the importance of adult-oriented health care.

On the other hand, most adult medical care providers, such as primary care physicians, in Japan are unfamiliar with CCS-specific care, and it is likely that some physicians in Japan are unaware of the existence of these types of high-risk populations.[17] Neither nurse practitioners nor general practitioners exist in Japan, whereas they play a central role in CCS care in Western countries. Increased dialog with not only CCS but also adult medical care providers, such as primary care physicians, on the importance of risk-based adult-oriented health care is needed continuously.

The limitations of our study were as follows: (i) the number of subjects was limited; (ii) patients with solid tumors were fewer than those with hematological cancers; (iii) a selection bias might be present when distributing the questionnaires because we didn't conduct random sampling; and (iv) we could not get incidence and time-to-event information because of the cross-sectional survey. But our report fills a niche in the published literature because there are few articles on medical visit behaviors of young adult CCS in Asian countries, including Japan.

Our study revealed that only just more than half of CCS prefer to continue to visit their previous treatment hospital with enough satisfaction in Japan. This key finding suggests that the medical transition to adult-oriented medical care is difficult and impractical now in Japan. To optimize risk-based care and promote health for CCS during adulthood, we should discuss the medical transition not only with CCS and their families but also with adult medical care providers, such as primary care physicians.

Acknowledgments

The institutions that provided patient data and recruited CCS to the survey are listed in the Appendix. We are grateful to Dr Gautam A. Deshpande (MD, a visiting researcher of St. Luke's International Hospital) for English editing of this manuscript.